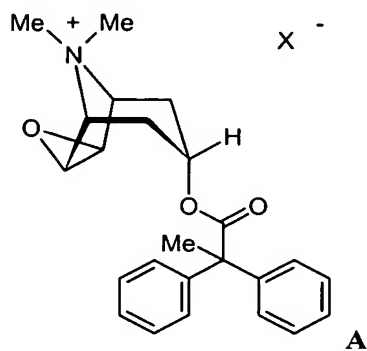


Patent Claims

- 1) A Pharmaceutical composition comprising one or more anticholinergics of formula A



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wherein

- X⁻ denotes an anion (counter-ion), preferably an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methansulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate

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combined with one or more p38 kinase inhibitors (B), optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates and optionally together with a pharmaceutically acceptable excipient.

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- 2) The Pharmaceutical composition according to claim 1, wherein the active substances A and B are present either together in a single formulation or in two separate formulations.

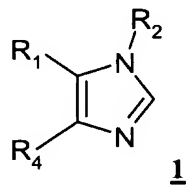
- 20 3) The Pharmaceutical composition according to claim 2, wherein for A X⁻ is selected from among chloride, bromide, methansulphonate and p-toluenesulphonate.

- 4) The Pharmaceutical composition according to claim 3, characterised in that in A X⁻ denotes bromide.
- 5) The Pharmaceutical composition according to claim 4, wherein the p38 kinase inhibitor B is selected from the group of compounds disclosed in US Patents 5,716,972, US 5,686,455, US 5,656,644, US 5,593,992, US 5,593,991, US 5,663,334, US 5,670,527, US 5,559,137, 5,658,903, US 5,739,143, US 5,756,499, US 6,277,989, US 6,340,685, and US 5,716,955 and PCT applications WO 92/12154, WO 94/19350, WO 95/09853, WO 95/09851, WO 95/09847, WO 95/09852, WO 97/25048, WO 97/25047, WO 97/33883, WO 97/35856, WO 97/35855, WO 97/36587, WO 97/47618, WO 97/16442, WO 97/16441, WO 97/12876, WO 98/25619, WO 98/06715, WO 98/07425, WO 98/28292, WO 98/56377, WO 98/07966, WO 98/56377, WO 98/22109, WO 98/24782, WO 98/24780, WO 98/22457, WO 98/52558, WO 98/52559, WO 98/52941, WO 98/52937, WO 98/52940, WO 98/56788, WO 98/27098, WO 98/47892, WO 98/47899, WO 98/50356, WO 98/32733, WO 99/58523, WO 99/01452, WO 99/01131, WO 99/01130, WO 99/01136, WO 99/17776, WO 99/32121, WO 99/58502, WO 99/58523, WO 99/57101, WO 99/61426, WO 99/59960, WO 99/59959, WO 99/00357, WO 99/03837, WO 99/01441, WO 99/01449, WO 99/03484, WO 99/15164, WO 99/32110, WO 99/32111, WO 99/32463, WO 99/64400, WO 99/43680, WO 99/17204, WO 99/25717, WO 99/50238, WO 99/61437, WO 99/61440, WO 00/26209, WO 00/18738, WO 00/17175, WO 00/20402, WO 00/01688, WO 00/07980, WO 00/07991, WO 00/06563, WO 00/12074, WO 00/12497, WO 00/31072, WO 00/31063, WO 00/23072, WO 00/31065, WO 00/35911, WO 00/39116, WO 00/43384, WO 00/41698, WO 00/69848, WO 00/26209, WO 00/63204, WO 00/07985, WO 00/59904, WO 00/71535, WO 00/10563, WO 00/25791, WO 00/55152, WO 00/55139, WO 00/17204, WO 00/36096, WO 00/55120, WO 00/55153, WO 00/56738, WO 01/21591, WO 01/29041, WO 01/29042, WO 01/62731, WO 01/05744, WO 01/05745, WO 01/05746, WO 01/05749, WO 01/05751, WO 01/27315, WO 01/42189, WO 01/00208, WO 01/42241, WO 01/34605, WO 01/47897, WO

01/64676, WO 01/37837, WO 01/38312, WO 01/38313, WO 01/36403, WO 01/38314, WO 01/47921, WO 01/27089, DE 19842833, and JP 2000 86657.

- 6) The Pharmaceutical composition according to claim 5, wherein the p38 kinase inhibitor **B** is selected from the group of compounds disclosed in US 6,277,989, US 6,340,685, WO 00/12074, WO 00/12497, WO 00/59904, WO 00/71535, WO 01/64676, WO 99/61426, WO 00/10563, WO 00/25791, WO 01/37837, WO 01/38312, WO 01/38313, WO 01/38314, WO 01/47921, WO 99/61437, WO 99/61440, WO 00/17175, WO 00/17204, WO 00/36096, WO 98/27098, WO 99/00357, WO 99/58502, WO 99/64400, WO 99/01131, WO 00/43384, WO 00/55152, WO 00/55139, and WO 01/36403.

- 7) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **1**

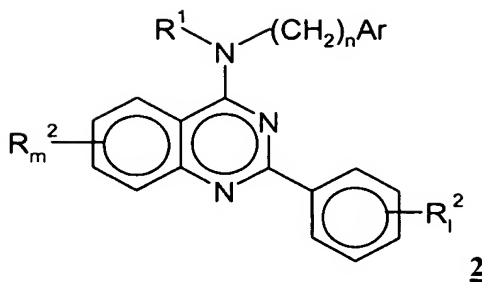


wherein

- R₁ is 4-pyridyl, pyrimidinyl, 4-pyridazinyl, 1,2,4-triazin-5-yl, quinolyl, isoquinolyl, or quinazolin-4-yl ring, which ring is substituted with Y-R_a and optionally with an additional independent substituent selected from C₁₋₄ alkyl, halogen, hydroxyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅, N(R₁₀)C(O)R_b or NHR_a;
- Y is oxygen or sulfur;
- R₄ is phenyl, naphth-1-yl or naphth—yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and

- which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, C(Z)NR₇R₁₇, C(Z)OR₁₆, (CR₁₀R₂₀)_vCOR₁₂, SR₅, SOR₅, OR₁₂, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, ZC(Z)R₁₂, NR₁₀C(Z)R₁₆, or (CR₁₀R₂₀)_vNR₁₀R₂₀ and which, for other positions of substitution, is halogen, cyano, C(Z)NR₁₃R₁₄, C(Z)OR₃, (CR₁₀R₂₀)_mCOR₃, S(O)_mR₃, OR₃, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, (CR₁₀R₂₀)_mR₁₀C(Z)R₃, NR₁₀S(O)_mR₈, NR₁₀S(O)_mNR₇R₁₇, ZC(Z)R₃ or (CR₁₀R₂₀)_mNR₁₃R₁₄;
- Z is oxygen or sulfur;
- n is an integer having a value of 1 to 10;
- 10 m is 0, or integer 1 or 2;
- m' is an integer having a value of 1 or 2;
- m'' is 0, or an integer having a value of 1 to 5;
- v is 0, or an integer having a value of 1 to 2;
- R₂ is -C(H) (A) (R₂₂);
- 15 A is optionally substituted aryl, heterocyclyl, or heteroaryl ring, or A is substituted C₁₋₁₀ alkyl;
- R₂₂ is an optionally substituted C₁₋₁₀ alkyl;
- R_a is aryl, arylC₁₋₆ alkyl, heterocyclic, heterocyclylC₁₋₆ alkyl, heteroaryl, heteroarylC₁₋₆alkyl, wherein each of these moieties may be optionally substituted;
- 20 R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, aryl C₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl, wherein each of these moieties may be optionally substituted;
- R₃ is heterocyclyl, heterocyclyl C₁₋₁₀ alkyl or R₈;
- R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇, excluding the moieties SR₅ being SNR₇R₁₇ and SOR₅ being SOH;
- 25 R₆ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, aryl C₁₋₄ alkyl, heteroaryl, heteroaryl C₁₋₄ alkyl, heterocyclyl, aryl, or C₁₋₁₀ alkanoyl;
- R₇ and R₁₇ is each independently selected from hydrogen or C₁₋₄ alkyl or R₇ and R₁₇ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅;
- 30

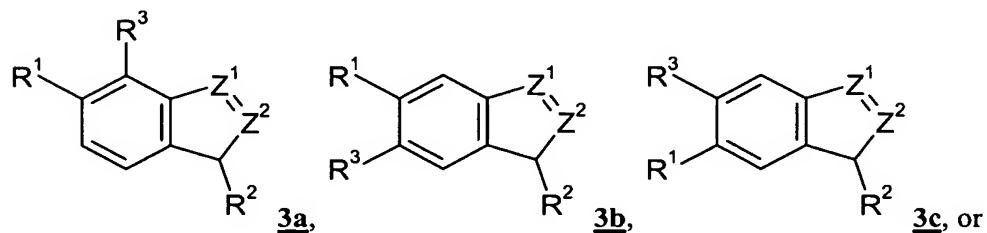
- R₈ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, aryl C₁₋₁₀ alkyl, heteroaryl, heteroaryl C₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nNR₁₃R₁₄; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;
- R₉ is hydrogen, C(Z) R₁₁ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₁₈, optionally substituted aryl or optionally substituted aryl C₁₋₄ alkyl;
- R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₄ alkyl;
- R₁₁ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroaryl C₁₋₁₀ alkyl, wherein these moieties may be optionally substituted;
- R₁₂ is hydrogen or R₁₆;
- R₁₃ and R₁₄ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted arylC₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉;
- R₁₅ is R₁₀ or C(Z)-C₁₋₄ alkyl;
- R₁₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;
- R₁₈ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, aryl₁₋₁₀ alkyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroaryl₁₋₁₀ alkyl;
- or a pharmaceutically acceptable salt thereof.
- 8) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **2**

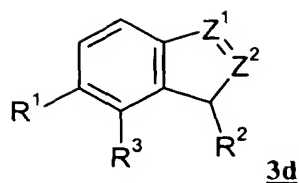


wherein

- R^1 is H, alkyl(1-6C) or arylalkyl optionally substituted on the aryl group with 1-3 substituents independently selected from alkyl (1-6C), halo, OR, NR_2 , SR, -OOCR, -NROCR, RCO, -COOR, -CONR₂, -SO₂NR₂, CN, CF₃, and NO₂,
 5 wherein each R is independently H or lower alkyl (1-4C);
 each R^2 is independently alkyl (1-6C), halo, OR, SR, OOCR, NROCR, COOR, RCO, CONR₂, SO₂NR₂, CN, CF₃ or NO₂, wherein each R is independently H or lower alkyl (1-4C);
 10 each of l, m, and n is independently 0, 1 or 2; and
 Ar is phenyl, 2-, 3- or 4-pyridyl, indolyl, 2- or 4-pyrimidyl, or benzimidazolyl, each optionally substituted with optionally substituted alkyl, alkenyl, alkynyl, aryl, N-aryl, NH-aroyl, halo, OR, NR_2 , SR, -OOCR, -NROCR, RCO, -COOR, -CONR₂, SO₂NR₂, CN, CF₃, or NO₂, wherein each R is independently H or alkyl (1-4C), or
 15 the pharmaceutically acceptable salts thereof.

- 9) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **3a**, **3b**, **3c**, or **3d**





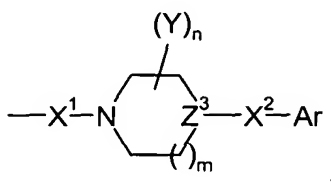
and the pharmaceutically acceptable salts thereof,

wherein each of Z^1 and Z^2 is independently CR^4 or N;

where each R^4 is independently selected from H and alkyl(1-6C);

- 5 wherein said alkyl optionally includes one or more heteroatoms selected from O, S and N,
 and wherein said alkyl is optionally substituted by one or more substituents selected
 from halo, OR, SR, NR_2 , RCO, COOR, $CONR_2$, OOCR, NROCR, CN, =O, a 5 or 6
 membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a 6-
 membered aromatic ring optionally containing 1-2 N heteroatoms, wherein R in the
 10 foregoing optional substituents is H or alkyl (1-6C);

R^1 is



wherein

X^1 is CO, SO, CHOH or SO_2 ;

- 15 m is 1;

Y is optionally substituted alkyl, optionally substituted aryl, or optionally substituted
 arylalkyl;

n is 0, 1 or 2;

Z^3 is N;

- 20 X^2 is CH or CH_2 ; and

Ar consists of one or two phenyl moieties directly coupled to X^2 , said one or two phenyl
 moieties being optionally substituted by a substituent selected from halo, nitro, alkyl
 (1-6C), alkenyl (1-6C), CN, CF_3 , RCO, COOR, $CONR_2$, NR_2 , OR, SR, OOCR,

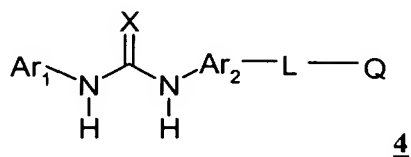
NROCR, (wherein R in the foregoing is H or 1-6C alkyl), and phenyl, itself optionally substituted by the foregoing substituents;

R² is selected from H, and alkyl (1-6C);

wherein said alkyl optionally includes one or more heteroatoms which are selected from O, S and N, and wherein said alkyl is optionally substituted by one or more substituents selected from halo, OR, SR, NR₂, RCO, COOR, CONR₂, OOCR, NROCR, (where R in the foregoing is H or 1-6C alkyl) CN, =O, a 5 or 6 membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a 6-membered aromatic ring optionally containing 1-2 N heteroatoms;

R³ is H, halo, NO₂, alkyl (1-6C), alkenyl (1-6C), CN, OR, SR, NR₂, RCO, COOR, CONR₂, OOCR, or NROCR where R is H or alkyl (1-6C).

10) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **4**



wherein

Ar₁ is a heterocyclic group selected from the group consisting of pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and thiophene; and wherein Ar₁ may be substituted by one or more R₁, R₂ or R₃;

Ar₂ is phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline, tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl or indole each being optionally substituted with one to three R₂ groups;

L, a linking group, is a C₁₋₁₀ saturated or unsaturated branched or unbranched carbon chain;

wherein one or more methylene groups are optionally independently replaced by O,N or S; and

wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl which may be substituted by one or more halogen atoms;

Q is selected from the group consisting of:

a) phenyl, naphthyl, pyridine, pyrimidine, pyridazine, imidazole, benzimidazole, furan, thiophene, pyran, naphthyridine, oxazo[4,5-*b*]pyridine and imidazo[4,5-*b*]pyridine, which are optionally substituted with one to three groups selected from the group consisting of halogen,

C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m and phenylamino wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C₁₋₆ alkyl and C₁₋₆ alkoxy;

b) tetrahydropyran, tetrahydrofuran, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine sulfoxide, thiomorpholine sulfone, piperidine, piperidinone, tetrahydropyrimidone, cyclohexanone, cyclohexanol, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone which are optionally substituted with one to three groups selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, mono- or di-(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, phenylamino-C₁₋₃ alkyl and C₁₋₃ alkoxy-C₁₋₃ alkyl;

c) C₁₋₆ alkoxy, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C₁₋₃ alkyl and C₁₋₅ alkoxyalkyl and phenyl wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_r, phenyl-S(O)_t, wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino;

R₁ is selected from the group consisting of:

- a) C₃₋₁₀ branched or unbranched alkyl, which may optionally be partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle selected from the group hereinabove described, being substituted with 0 to 5 groups selected from the group consisting of halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, C₃₋₈ cycloalkyl, C₅₋₈ cycloalkenyl, hydroxy, cyano, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, NH₂C(O) and di(C₁₋₃)alkylaminocarbonyl;
- b) C₃₋₇ cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which may optionally be partially or fully halogenated and which may optionally be substituted with one to three C₁₋₃ alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from O, S, CHOH, >C=O, >C=S and NH;
- c) C₃₋₁₀ branched alkenyl which may optionally be partially or fully halogenated, and which is optionally substituted with one to three C₁₋₅ branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, hydroxy, cyano, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, NH₂C(O), mono- or di(C₁₋₃)alkylaminocarbonyl;
- d) C₅₋₇ cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl,

wherein such cycloalkenyl group may optionally be substituted with one to three C₁₋₃ alkyl groups;

e) cyano; and,

f) methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

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R₂ is selected from the group consisting of:

a C₁₋₆ branched or unbranched alkyl which may optionally be partially or fully halogenated, acetyl, aroyl, C₁₋₄ branched or unbranched alkoxy, which may optionally be partially or fully halogenated, halogen, methoxycarbonyl and phenylsulfonyl;

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R₃ is selected from the group consisting of:

a) a phenyl, naphthyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl; wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a C₁₋₆ branched or unbranched alkyl, phenyl, naphthyl, heterocycle selected from the group hereinabove described, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halo, hydroxy, cyano, C₁₋₃ alkyloxy which may optionally be partially or fully halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅

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alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋₃)alkylamino-S(O)₂, R₄-C₁₋₅ alkyl, R₅-C₁₋₅ alkoxy, R₆-C(O)-C₁₋₅ alkyl and R₇-C₁₋₅ alkyl(R₈)N;

b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from the group consisting of cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanthiophene and cyclohexanthiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl and heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₄ alkyl-OC(O), C₁₋₅ alkyl-C(O)-C₁₋₄ branched or unbranched alkyl, an amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, R₉-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkoxy, R₁₁-C(O)-C₁₋₅ alkyl, and R₁₂-C₁₋₅ alkyl(R₁₃)N;

c) cycloalkyl selected from the group consisting of cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which the cycloalkyl may optionally be partially or fully halogenated and which may optionally be substituted with one to three C₁₋₃ alkyl groups;

- d) C₅₋₇ cycloalkenyl, selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group may optionally be substituted with one to three C₁₋₃ alkyl groups; and
- 5 e) acetyl, aroyl, alkoxycarbonylalkyl or phenylsulfonyl;
- f) C₁₋₆ branched or unbranched alkyl which may optionally be partially or fully halogenated;

or R₁ and R₂ taken together may optionally form a fused phenyl or pyridinyl ring,

10 and wherein each R₈, R₁₃ is independently selected from the group consisting of:
hydrogen and C₁₋₄ branched or unbranched alkyl which may optionally be partially or fully halogenated;

15 each R₄, R₅, R₆, R₇, R₉, R₁₀, R₁₁ and R₁₂ is independently selected from the group consisting of:
morpholine, piperidine, piperazine, imidazole and tetrazole;

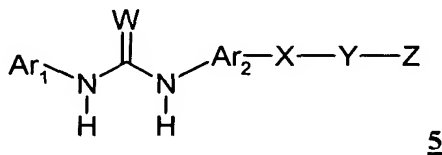
m = 0, 1, 2;

20 r = 0, 1, 2;

t = 0, 1, 2;

X = O or S and physiologically acceptable acids or salts thereof.

- 25 11) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula 5



wherein:

Ar₁ is selected from the group consisting of:
pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and thiophene;
wherein Ar₁ may be substituted by one or more R₁, R₂ or R₃;

5

Ar₂ is:
phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline,
tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl or indole each
being optionally substituted with zero to three R₂ groups;

10

X is:
a) a C₅₋₈ cycloalkyl or cycloalkenyl optionally substituted with 0-2 oxo groups or
0-3 C₁₋₄ branched or unbranched alkyl, C₁₋₄ alkoxy or C₁₋₄ alkylamino chains;
b) phenyl, furan, thiophene, pyrrole, imidazolyl, pyridine, pyrimidine, pyridinone,
dihydropyridinone, maleimide, dihydromaleimide, piperdine, piperazine or
pyrazine each being optionally independently substituted with 0-3 C₁₋₄
branched or unbranched alkyl, C₁₋₄alkoxy, hydroxy, nitrile, mono- or di-(C₁₋₃
alkyl)amino, C₁₋₆ alkyl-S(O)_m, or halogen;

15

20 Y is:
a bond or a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain
optionally partially or fully halogenated, wherein one or more methylene groups are
optionally replaced by O, NH, S(O), S(O)₂ or S and wherein Y is optionally
independently substituted with 0-2 oxo groups and one or more C₁₋₄ branched or
25 unbranched alkyl which may be substituted by one or more halogen atoms;

25

Z is:
a) phenyl, pyridine, pyrimidine, pyridazine, imidazole, furan, thiophene, pyran,
which are optionally substituted with one to three groups consisting of halogen,
C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-
S(O)_m, COOH and phenylamino wherein the phenyl ring is optionally
30

30

- substituted with one to two groups consisting of halogen, C₁₋₆ alkyl and C₁₋₆ alkoxy;
- 5 b) tetrahydropyran, tetrahydrofuran, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine sulfoxide, piperidine, piperidinone, piperazine, tetrahydropyrimidone, cyclohexanone, cyclohexanol, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide or tetramethylene sulfone which are optionally substituted with one to three groups consisting of nitrile, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, mono- or di-(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, phenylamino-C₁₋₃ alkyl and C₁₋₃ alkoxy-C₁₋₃ alkyl;
- 10 c) C₁₋₆ alkoxy, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C₁₋₃ alkyl, C₁₋₅ alkoxyalkyl, pyridinyl-C₁₋₃ alkyl, imidazolyl-C₁₋₃ alkyl, tetrahydrofuranyl-C₁₋₃ alkyl, phenylamino, wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, and phenyl-S(O)_m, wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino;
- 15
- 20 R₁ is :
- a) C₃₋₁₀ branched or unbranched alkyl optionally partially or fully halogenated and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle selected from the group hereinabove described in this paragraph, and being substituted with 0 to 5 groups selected from the group consisting of halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, C₃₋₈ cycloalkyl, C₅₋₈ cycloalkenyl, hydroxy, nitrile, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, NH₂C(O) and di(C₁₋₃)alkylaminocarbonyl;
- 25
- 30

- 5 b) C₃₋₇ cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl each being optionally be partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from the group consisting of O, S, CHOH, >C=O, >C=S and NH;
- 10 c) C₃₋₁₀ branched alkenyl optionally partially or fully halogenated and optionally substituted with one to three C₁₋₅ branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from the group consisting of halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, hydroxy, nitrile, C₁₋₃ alkoxy which is optionally partially or fully halogenated, NH₂C(O) and mono- or
- 15 di(C₁₋₃)alkylaminocarbonyl;
- 20 d) a C₅₋₇ cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C₁₋₃ alkyl groups;
- 25 e) nitrile; or
- f) C₁₋₆ branched or unbranched alkoxy carbonyl, C₁₋₆ branched or unbranched alkylaminocarbonyl, C₁₋₆ branched or unbranched alkylcarbonylamino-C₁₋₃-alkyl;

30 R₂ is:

a C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C₁₋₄ branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl or phenylsulfonyl;

5 R₃ is:

- a) phenyl, naphthyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl, wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of phenyl, naphthyl, heterocycle selected from the group hereinabove described in this paragraph, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl, bicycloheptyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halogen, hydroxy, nitrile, C₁₋₃ alkyloxy which may optionally be partially or fully halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described in this paragraph, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋₃)alkylamino-S(O)₂, R₄-C₁₋₅ alkyl, R₅-C₁₋₅ alkoxy, R₆-C(O)-C₁₋₅ alkyl and R₇-C₁₋₅ alkyl(R₈)N, carboxy-mono- or di-(C₁₋₅)-alkyl-amino;
- b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from the group consisting
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- of cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanthiophene and cyclohexanthiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from the group consisting of phenyl, naphthyl and heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, halogen, nitrile, C₁₋₃ alkoxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₄ alkyl-OC(O), C₁₋₅ alkyl-C(O)-C₁₋₄ branched or unbranched alkyl, an amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, R₉-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkoxy, R₁₁-C(O)-C₁₋₅ alkyl, and R₁₂-C₁₋₅ alkyl(R₁₃)N;
- c) cycloalkyl selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl and bicycloheptyl, wherein the cycloalkyl is optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups;
- d) C₅₋₇ cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C₁₋₃ alkyl groups;

- e) acetyl, aroyl, alkoxycarbonylalkyl or phenylsulfonyl; or
- f) C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated;

or R₁ and R₂ taken together may optionally form a fused phenyl or pyridinyl ring;

5

each R₈ and R₁₃ is independently selected from the group consisting of:

hydrogen and C₁₋₄ branched or unbranched alkyl optionally be partially or fully halogenated;

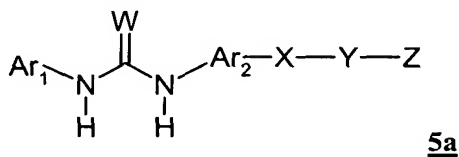
- 10 each R₄, R₅, R₆, R₇, R₉, R₁₀, R₁₁ and R₁₂ is independently selected from the group consisting of morpholine, piperidine, piperazine, imidazole and tetrazole;

m is 0, 1 or 2;

W is O or S and pharmaceutically acceptable derivatives thereof.

15

12) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **5a**



20

wherein:

Ar₁ is:

pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and thiophene;

25

wherein Ar₁ is optionally substituted by one or more R₁, R₂ or R₃;

Ar₂ is:

phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline, tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl and indole each being optionally substituted with zero to three R_2 groups;

5 X is:

a C_{5-8} cycloalkyl or cycloalkenyl optionally substituted with one to two oxo groups or one to three C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} alkylamino chains each being branched or unbranched;

10 phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, tetrahydropyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdinyl, benzimidazole, 3H-imidazo[4,5-b]pyridine, piperazinyl, pyridazinyl or pyrazinyl; each being optionally independently substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, nitrile, amino, mono-
15 or di- $(C_{1-3}$ alkyl)amino, mono- or di- $(C_{1-3}$ alkylamino)carbonyl, $NH_2C(O)$, C_{1-6} alkyl-S(O) $_m$ or halogen;

Y is:

a bond or a C_{1-4} saturated or unsaturated branched or unbranched carbon chain
20 optionally partially or fully halogenated, wherein one or more C atoms are optionally replaced by O, N, or S(O) $_m$ and wherein Y is optionally independently substituted with one to two oxo groups, nitrile, phenyl, hydroxy or one or more C_{1-4} alkyl optionally substituted by one or more halogen atoms;

25 Z is:

aryl, indanyl, heteroaryl selected from benzimidazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl and pyranal, heterocycle selected from piperazinyl, tetrahydropyrimidinyl, cyclohexanonyl, cyclohexanolyl, 2-oxa- or 2-thia-5-aza-bicyclo[2.2.1]heptanyl,
30 pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl or tetramethylene sulfonyl,

tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholino, thiomorpholino, thiomorpholino sulfoxidyl, thiomorpholino sulfonyl, piperidinyl, piperidinonyl, pyrrolidinyl and dioxolanyl,
each of the aforementioned Z are optionally substituted with one to three halogen,
5 C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₃ alkoxy-C₁₋₃ alkyl, C₁₋₆ alkoxycarbonyl, aroyl, heteroaroyl, heterocycleC₁₋₃acyl wherein the heteroaryl and heterocycle are as defined hereinabove in this paragraph, C₁₋₃acyl, oxo, hydroxy, pyridinyl-C₁₋₃ alkyl, imidazolyl-C₁₋₃ alkyl, tetrahydrofuranyl-C₁₋₃ alkyl, nitrile-C₁₋₃ alkyl, nitrile, carboxy, phenyl wherein the phenyl ring is optionally substituted with one to two
10 halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino, amino-S(O)_m, C₁₋₆ alkyl-S(O)_m or phenyl-S(O)_m wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy, halogen or mono- or di-(C₁₋₃ alkyl)amino;
or Z is optionally substituted with one to three amino, aminocarbonyl or amino-C₁₋₃
15 alkyl wherein the N atom is optionally independently mono- or di-substituted by aminoC₁₋₆alkyl, C₁₋₃alkyl, arylC₀₋₃alkyl, C₁₋₅ alkoxyC₁₋₃ alkyl, C₁₋₅ alkoxy, aroyl, C₁₋₃acyl, C₁₋₃alkyl-S(O)_m- or arylC₀₋₃alkyl-S(O)_m- each of the aforementioned alkyl and aryl attached to the amino group is optionally substituted with one to two halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino;
20 or Z is optionally substituted with one to three aryl, heterocycle or heteroaryl as hereinabove described in this paragraph each in turn is optionally substituted by halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;
or Z is hydroxy, hydroxyC₁₋₃alkyl, halogen, nitrile, amino wherein the N atom is optionally independently mono- or di-substituted by C₁₋₆alkyl, aminoC₁₋₆alkyl,
25 arylC₀₋₃alkyl, C₁₋₅ alkoxyC₁₋₃ alkyl, C₁₋₅ alkoxy, aroyl, C₁₋₃acyl, C₁₋₃alkyl-S(O)_m- , arylC₀₋₃alkyl-S(O)_m- , nitrileC₁₋₄alkyl or C₁₋₃alkoxyC₁₋₃alkyl, each of the aforementioned alkyl and aryl attached to the amino group is optionally substituted with one to two halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkoxyheteroarylC₀₋₃alkyl, heteroarylC₀₋₃alkyl or
30 heterocycleC₀₋₃alkyl wherein the heteroaryl and heterocycle is hereinabove described in this paragraph,

or Z is C₁₋₆alkyl branched or unbranched, C₁₋₆alkoxy, C₁₋₃acylamino, nitrileC₁₋₄alkyl, C₁₋₆ alkyl-S(O)_m, and phenyl-S(O)_m, wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino;

5

R₁ is :

- a) C₁₋₁₀ branched or unbranched alkyl optionally partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle, selected from the group hereinabove described, being substituted with 0 to 5 groups selected from the group consisting of halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, C₃₋₈ cycloalkyl, C₅₋₈ cycloalkenyl, hydroxy, nitrile, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, NH₂C(O) and di(C₁₋₃)alkylaminocarbonyl;
- b) C₃₋₇ cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl and bicycloheptyl, each optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from the group consisting of O, S, CHOH, >C=O, >C=S and NH;
- c) C₃₋₁₀ branched alkenyl optionally partially or fully halogenated and optionally substituted with one to three C₁₋₅ branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from the group consisting of halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or

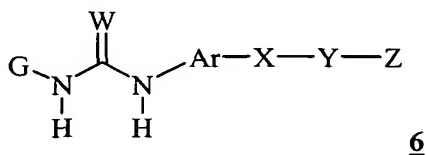
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- fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, hydroxy, nitrile, C₁₋₃ alkoxy which is optionally partially or fully halogenated, NH₂C(O) and mono- or
- 5 di(C₁₋₃)alkylaminocarbonyl;
- d) a C₅₋₇ cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C₁₋₃ alkyl groups;
- 10 e) nitrile; or
- f) C₁₋₆ branched or unbranched alkoxy carbonyl, C₁₋₆ branched or unbranched alkylaminocarbonyl, C₁₋₆ branched or unbranched alkylcarbonylamino-C₁₋₃-alkyl;
- 15 R₂ is:
- a C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated and optionally substituted with nitrile,
- or R₂ is acetyl, aroyl, C₁₋₄ branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl or phenylsulfonyl;
- 20 R₃ is:
- a) phenyl, naphthyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl,
- 25 isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl, wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a
- 30 phenyl, naphthyl, heterocycle selected from the group hereinabove described in this paragraph, C₁₋₆ branched or unbranched alkyl which is optionally partially

- or fully halogenated, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl, bicycloheptyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halogen, hydroxy, oxo, nitrile, C₁₋₃ alkoxy optionally partially or fully halogenated,
- 5 C₁₋₃ alkoxyC₁₋₅alkyl, C₁₋₃thioalkyl, C₁₋₃thioalkylC₁₋₅alkyl, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described in this paragraph, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described in
- 10 this paragraph, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋₃)alkylamino-S(O)₂, R₄-C₁₋₅ alkyl, R₅-C₁₋₅ alkoxy, R₆-C(O)-C₁₋₅ alkyl and R₇-C₁₋₅ alkyl(R₈)N, carboxy-mono- or di-(C₁₋₅)-alkyl-amino;
- 15 b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from the group consisting of cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine,
- 20 cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole,
- 25 cyclopentanothiophene and cyclohexanothiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from the group consisting of phenyl, naphthyl and heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C₁₋₆
- 30 branched or unbranched alkyl which is optionally partially or fully halogenated, halogen, nitrile, C₁₋₃ alkoxy which is optionally partially or fully

- halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₄ alkyl-OC(O), C₁₋₅ alkyl-C(O)-C₁₋₄ branched or unbranched alkyl, an amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, R₉-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkoxy, R₁₁-C(O)-C₁₋₅ alkyl and R₁₂-C₁₋₅ alkyl(R₁₃)N;
- 5
- c) cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl and bicycloheptyl, wherein the cycloalkyl is optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups;
- 10
- d) C₅₋₇ cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C₁₋₃ alkyl groups;
- 15
- e) acetyl, aroyl, C₁₋₆alkoxycarbonylC₁₋₆alkyl or phenylsulfonyl; or
- f) C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated;
- 20 or R₁ and R₂ taken together optionally form a fused phenyl or pyridinyl ring;
- each R₈ and R₁₃ is independently selected from the group consisting of: hydrogen and C₁₋₄ branched or unbranched alkyl optionally partially or fully halogenated;
- 25 each R₄, R₅, R₆, R₇, R₉, R₁₀, R₁₁ and R₁₂ is independently selected from the group consisting of morpholine, piperidine, piperazine, imidazole and tetrazole;
- m is 0, 1 or 2;
- W is O or S;
- 30 wherein X is directly attached to one or two -Y-Z, and pharmaceutically acceptable derivatives thereof.

13) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **6**



wherein:

G is :

an aromatic C₆₋₁₀ carbocycle or a nonaromatic C₃₋₁₀ carbocycle saturated or unsaturated;

a 6-10 membered heteroaryl containing 1 or more heteroatoms chosen from O, N and S;

a 5-8 membered monocyclic heterocycle containing one or more heteroatoms chosen from O, N and S;

or

an 8-11 membered bicyclic heterocycle, containing one or more heteroatoms chosen from O, N and S;

wherein G is substituted by one or more R₁, R₂ or R₃;

Ar is:

phenyl, naphthyl, quinoliny, isoquinoliny, tetrahydronaphthyl, tetrahydroquinoliny, tetrahydroisoquinoliny, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, indoliny, benzothienyl, dihydrobenzothienyl, indanyl, indenyl or indolyl each being optionally substituted by one or more R₄ or R₅;

X is:

a C₅₋₈ cycloalkyl or cycloalkenyl optionally substituted with one to two oxo groups or one to three C₁₋₄ alkyl, C₁₋₄ alkoxy or C₁₋₄ alkylamino chains;

phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdinyl, benzimidazole, 3H-imidazo[4,5-b]pyridine, piperazinyl, pyridazinyl or pyrazinyl;

5

Y is:

a bond or a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, N, or S(O)_m and wherein Y is optionally independently substituted with one to two oxo groups, phenyl or one or more C₁₋₄ alkyl optionally substituted by one or more halogen atoms;

10

Z is:

phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, pyranyl each being optionally substituted with one to three halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, amino, mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, CN, CONH₂, COOH or phenylamino wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;

15

tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, thiomorpholino sulfoxidyl, thiomorpholino sulfonyl, piperidinyl, piperidinonyl, piperazinyl, tetrahydropyrimidinonyl, cyclohexanonyl, cyclohexanolyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfide, tetramethylene sulfoxidyl or tetramethylene sulfonyl each being optionally substituted with one to three nitrile, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, amino, mono- or di-(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, CONH₂, phenylamino-C₁₋₃ alkyl or C₁₋₃ alkoxy-C₁₋₃ alkyl;

20

halogen, C₁₋₄ alkyl, nitrile, amino, hydroxy, C₁₋₆ alkoxy, NH₂C(O), mono- or di(C₁₋₃ alkyl) aminocarbonyl, mono- or di(C₁₋₆alkyl)amino, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to C₁₋₃ alkyl or C₁₋₅ alkoxyalkyl,

30

pyridinyl-C₁₋₃ alkyl, imidazolyl-C₁₋₃ alkyl, tetrahydrofuranyl-C₁₋₃ alkyl, nitrile-C₁₋₃ alkyl, carboxamide-C₁₋₃ alkyl, phenyl, wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, or phenyl-S(O)_m, wherein the phenyl ring is
 5 optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy, halogen or mono- or di-(C₁₋₃ alkyl)amino;
 C₁₋₆ alkyl-S(O)_m, and phenyl-S(O)_m, wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino;

10

each R₁ is independently:

C₁₋₁₀ alkyl optionally be partially or fully halogenated, and optionally substituted with one to three C₃₋₁₀ cycloalkanyl, hydroxy, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl,
 15 isoxazolyl or isothiazolyl; each of the aforementioned being optionally substituted with one to five groups selected from halogen, C₁₋₆ alkyl which is optionally partially or fully halogenated, C₃₋₈ cycloalkanyl, C₅₋₈ cycloalkenyl, hydroxy, nitrile, C₁₋₃ alkoxy which is optionally partially or fully halogenated or NH₂C(O), mono- or di-(C₁₋₃alkyl)amino, and mono- or di-(C₁₋₃alkyl)aminocarbonyl;

20

cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, or cycloheptyloxy each being optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, CN, hydroxyC₁₋₃alkyl or aryl; or an analog of such cycloalkyl group wherein one to
 25 three ring methylene groups are independently replaced by O, S(O)_m, CHOH, >C=O, >C=S or NH;

phenyloxy or benzyloxy each being optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or
 30 fully halogenated, CN, hydroxyC₁₋₃alkyl or aryl; or an analog of such cycloaryl group wherein one to two ring methyne groups are independently replaced by N;

cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, CN, hydroxyC₁₋₃alkyl or aryl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S(O)_m, CHOH, >C=O, >C=S or NH;

C₃₋₁₀ branched or unbranched alkenyl each being optionally partially or fully halogenated, and optionally be substituted with one to three C₁₋₅ branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl or isothiazolyl, each of the aforementioned being substituted with zero to five halogen, C₁₋₆ alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, hydroxy, nitrile, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, NH₂C(O), mono- or di(C₁₋₃alkyl)aminocarbonyl; the C₃₋₁₀ branched or unbranched alkenyl being optionally interrupted by one or more heteroatoms chosen from O, N and S(O)_m;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C₁₋₃ alkyl groups;

nitrile, halogen;

methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

silyl containing three C₁₋₄ alkyl groups optionally partially or fully halogenated;

C₃₋₆ alkynyl branched or unbranched carbon chain optionally partially or fully

halogenated, wherein one or more methylene groups are optionally replaced by O, NH or S(O)_m and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, pyrrolidinyl, pyrrolyl, one or more C₁₋₄ alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, 5 piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C₁₋₃alkyl)amino optionally substituted by one or more halogen atoms;

each R₂, R₄, and R₅ is

a C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated, 10 acetyl, aroyl, C₁₋₄ branched or unbranched alkoxy, each being optionally partially or fully halogenated, halogen, nitrile, methoxycarbonyl, C₁₋₃ alkyl-S(O)_m optionally partially or fully halogenated, or phenylsulfonyl;

C₁₋₆ alkoxy, hydroxy, amino, or mono- or di-(C₁₋₄ alkyl)amino, nitrile, halogen; 15

OR₆;

nitro; or

20 mono- or di-(C₁₋₄ alkyl)amino-S(O)₂ optionally partially or fully halogenated, or H₂NSO₂;

each R₃ is independently:

25 phenyl, naphthyl, morpholinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, triazolyl, tetrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl or indazolyl, each of the 30 aforementioned is optionally substituted with one to three phenyl, naphthyl, heterocycle or heteroaryl as hereinabove described in this paragraph, C₁₋₆ branched

or unbranched alkyl which is optionally partially or fully halogenated,
 cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl,
 bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅
 alkyl, halogen, hydroxy, oxo, nitrile, C₁₋₃ alkyloxy optionally partially or fully
 5 halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocyclicoxy wherein
 the heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph,
 nitro, amino, mono- or di-(C₁₋₃alkyl)amino, phenylamino, naphthylamino,
 heteroaryl or heterocyclic amino wherein the heteroaryl heterocyclic moiety is as
 hereinabove described in this paragraph, NH₂C(O), a mono- or di-(C₁₋₃alkyl)
 10 aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃
 alkyl)amino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋₃alkyl)amino-S(O)₂, R₇-C₁₋₅ alkyl, R₈-
 C₁₋₅ alkoxy, R₉-C(O)-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkyl(R₁₁)N, carboxy-mono- or di-(C₁₋₅
 alkyl)-amino;

15 a fused aryl selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl,
 tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused
 heteroaryl selected from cyclopentenopyridinyl, cyclohexanopyridinyl,
 cyclopentanopyrimidinyl, cyclohexanopyrimidinyl, cyclopentanopyrazinyl,
 cyclohexanopyrazinyl, cyclopentanopyridazinyl, cyclohexanopyridazinyl,
 20 cyclopentanoquinolinyl, cyclohexanoquinolinyl, cyclopentanoisoquinolinyl,
 cyclohexanoisoquinolinyl, cyclopentanoindolyl, cyclohexanoindolyl,
 cyclopentanobenzimidazolyl, cyclohexanobenzimidazolyl,
 cyclopentanobenzoxazolyl, cyclohexanobenzoxazolyl, cyclopentanoimidazolyl,
 cyclohexanoimidazolyl, cyclopentanothienyl and cyclohexanothienyl; wherein the
 25 fused aryl or fused heteroaryl ring is independently substituted with zero to three
 phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl,
 imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, C₁₋₆ alkyl which is
 optionally partially or fully halogenated, halogen, nitrile, C₁₋₃ alkyloxy which is
 optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or
 30 heterocyclicoxy wherein the heteroaryl or heterocyclic moiety is as hereinabove
 described in this paragraph, nitro, amino, mono- or di-(C₁₋₃alkyl)amino,

phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, NH₂C(O), mono- or di-(C₁₋₃alkyl)aminocarbonyl, C₁₋₄ alkyl-OC(O), C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, R₁₂-C₁₋₅ alkyl, R₁₃-C₁₋₅ alkoxy, R₁₄-C(O)-C₁₋₅ alkyl or R₁₅-C₁₋₅ alkyl(R₁₆)N;

cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S, CHOH, >C=O, >C=S or NH;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, each optionally substituted with one to three C₁₋₃ alkyl groups;

C₁₋₄ alkyl-phenyl-C(O)-C₁₋₄ alkyl-, C₁₋₄ alkyl-C(O)-C₁₋₄ alkyl- or C₁₋₄ alkyl-phenyl-S(O)_m-C₁₋₄ alkyl-;

C₁₋₆ alkyl or C₁₋₆ branched or unbranched alkoxy each of which is optionally partially or fully halogenated or optionally substituted with R₁₇;

OR₁₈ or C₁₋₆ alkyl optionally substituted with OR₁₈;

amino or mono- or di-(C₁₋₅alkyl)amino optionally substituted with R₁₉;

R₂₀C(O)N(R₂₁)-, R₂₂O- or R₂₃R₂₄NC(O)-; R₂₆(CH₂)_mC(O)N(R₂₁)- or R₂₆C(O)(CH₂)_mN(R₂₁)-;

C₂₋₆alkenyl substituted by R₂₃R₂₄NC(O)-;

C₂₋₆ alkynyl branched or unbranched carbon chain, optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH, S(O)_m and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, pyrroldinyl, pyrrolyl, morpholinyl, piperidinyl, 5 piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl one or more C₁₋₄ alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C₁₋₄ alkyl)amino optionally substituted by one or more halogen atoms; or

10 aroyl;

R₆ is a:

C₁₋₄ alkyl optionally partially or fully halogenated and optionally substituted with R₂₆;

15 each R₇, R₈, R₉, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₇, R₁₉, R₂₅ and R₂₆ is independently: nitrile, phenyl, morpholino, piperidinyl, piperazinyl, imidazolyl, pyridinyl, tetrazolyl, amino or mono- or di-(C₁₋₄alkyl)amino optionally partially or fully halogenated;

20 each R₁₁ and R₁₆ is independently:

hydrogen or C₁₋₄ alkyl optionally partially or fully halogenated;

R₁₈ is independently:

25 hydrogen or a C₁₋₄ alkyl optionally independently substituted with oxo or R₂₅;

R₂₀ is independently:

C₁₋₁₀ alkyl optionally partially or fully halogenated, phenyl, or pyridinyl;

30 R₂₁ is independently:

hydrogen or C₁₋₃ alkyl optionally partially or fully halogenated;

each R₂₂, R₂₃ and R₂₄ is independently:

hydrogen, C₁₋₆ alkyl optionally partially or fully halogenated, said C₁₋₆ alkyl is optionally interrupted by one or more O, N or S, said C₁₋₆ alkyl also being independently optionally substituted by mono- or di-(C₁₋₃alkyl)aminocarbonyl, phenyl, pyridinyl, amino or mono- or di-(C₁₋₄alkyl)amino each of which is optionally partially or fully halogenated and optionally substituted with mono- or di-(C₁₋₃alkyl)amino;

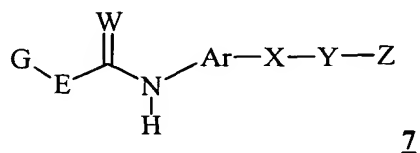
or R₂₃ and R₂₄ taken together optionally form a heterocyclic or heteroaryl ring;

m = 0, 1 or 2;

W is O or S and

pharmaceutically acceptable derivatives thereof.

14) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula 7



wherein:

E is carbon or a heteroatom group chosen from -O-, -NH- and -S-;

G is :

an aromatic C₆₋₁₀ carbocycle or a nonaromatic C₃₋₁₀carbocycle saturated or unsaturated;

a 6-14 membered monocyclic, bicyclic or tricyclic heteroaryl containing 1 or more heteroatoms chosen from O, N and S;

a 6-8 membered monocyclic heterocycle containing one or more heteroatoms chosen from O, N and S;

or

an 8-11 membered bicyclic heterocycle, containing one or more heteroatoms chosen from O, N and S;

wherein G is optionally substituted by one or more R₁, R₂ or R₃;

Ar is:

phenyl, naphthyl, quinoliny, isoquinoliny, tetrahydronaphthyl, tetrahydroquinoliny, tetrahydroisoquinoliny, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, indoliny, benzothienyl, dihydrobenzothienyl, indanyl, indenyl or indolyl each being optionally substituted by one or more R₄ or R₅;

X is:

a C₅₋₈ cycloalkyl or cycloalkenyl optionally substituted with one to two oxo groups or one to three C₁₋₄ alkyl, C₁₋₄ alkoxy or C₁₋₄ alkylamino chains each being branched or unbranched;

aryl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdiny, benzimidazole, 3H-imidazo[4,5-b]pyridine, piperazinyl, pyridazinyl or pyrazinyl; each being optionally independently substituted with one to three C₁₋₄ alkyl, C₁₋₄alkoxy, hydroxy, nitrile, amino, mono- or di-(C₁₋₃ alkyl)amino, mono- or di-(C₁₋₃ alkylamino)carbonyl, NH₂C(O), C₁₋₆ alkyl-S(O)_m or halogen;

Y is:

a bond or a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more C atoms are optionally replaced by O, N, or S(O)_m and wherein Y is optionally independently substituted with one to two oxo groups, nitrile, phenyl or one or more C₁₋₄ alkyl optionally substituted by one or more halogen atoms;

Z is:

- aryl, heteroaryl selected from pyridinyl, piperazinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl and pyranyl, heterocycle selected from tetrahydropyrimidinyl, cyclohexanonyl, cyclohexanolyl, 2-oxa- or 2-thia-5-aza-bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl or tetramethylene sulfonyl, tetrahydropyranal, tetrahydrofuranal, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholino, thiomorpholino, thiomorpholino sulfoxidyl, thiomorpholino sulfonyl, piperidinyl, piperidinonyl, pyrrolidinyl and dioxolanyl, each of the aforementioned Z are optionally substituted with one to three halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₃ alkoxy-C₁₋₃ alkyl, C₁₋₆ alkoxy-carbonyl, aroyl, C₁₋₃ acyl, oxo, hydroxy, pyridinyl-C₁₋₃ alkyl, imidazolyl-C₁₋₃ alkyl, tetrahydrofuranal-C₁₋₃ alkyl, nitrile-C₁₋₃ alkyl, nitrile, carboxy, phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, or phenyl-S(O)_m wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy, halogen or mono- or di-(C₁₋₃ alkyl)amino;
- or Z is optionally substituted with one to three amino or amino-C₁₋₃ alkyl wherein the N atom is optionally independently mono- or di-substituted by amino-C₁₋₆alkyl, C₁₋₃alkyl, arylC₀₋₃alkyl, C₁₋₅ alkoxyC₁₋₃ alkyl, C₁₋₅ alkoxy, aroyl, C₁₋₃acyl, C₁₋₃alkyl-S(O)_m- or arylC₀₋₃alkyl-S(O)_m- each of the aforementioned alkyl and aryl attached to the amino group is optionally substituted with one to two halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;
- or Z is optionally substituted with one to three aryl, heterocycle or heteroaryl as hereinabove described in this paragraph each in turn is optionally substituted by halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;
- or Z is hydroxy, halogen, nitrile, amino wherein the N atom is optionally independently mono- or di-substituted by C₁₋₃acyl, C₁₋₆alkyl or C₁₋₃alkoxyC₁₋₃alkyl, C₁₋₆alkyl branched or unbranched, C₁₋₆alkoxy,

C₁₋₃acylamino, nitrileC₁₋₄alkyl, C₁₋₆ alkyl-S(O)_m, and phenyl-S(O)_m, wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino;

5 each R₁ is independently:

C₁₋₁₀ alkyl branched or unbranched optionally partially or fully halogenated, wherein one or more C atoms are optionally independently replaced by O, N or S(O)_m, and wherein said C₁₋₁₀ alkyl is optionally substituted with one to three C₃₋₁₀ cycloalkyl, hydroxy, oxo, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, thienyl, furyl, dioxolanyl, isoxazolyl or isothiazolyl; each of the aforementioned being optionally substituted with one to five groups selected from halogen, C₁₋₆ alkyl which is optionally partially or fully halogenated, C₃₋₈ cycloalkanyl, C₅₋₈ cycloalkenyl, hydroxy, nitrile, C₁₋₃ alkoxy which is optionally partially or fully halogenated or NH₂C(O), mono- or di(C₁₋₃alkyl)amino, and mono- or di(C₁₋₃alkyl)aminocarbonyl;

15 or R₁ is

cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, or cycloheptyloxy each being optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC₁₋₃alkyl or aryl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S(O)_m, CHOH, >C=O, >C=S or NH;

25 phenyloxy or benzyloxy each being optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC₁₋₃alkyl or aryl; or an analog of such cycloaryl group wherein one to two ring methyne groups are independently replaced by N;

30 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl optionally

partially or fully halogenated, nitrile, hydroxyC₁₋₃alkyl or aryl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S(O)_m, CHOH, >C=O, >C=S or NH;

5 C₃₋₁₀ branched or unbranched alkenyl each being optionally partially or fully halogenated, and optionally substituted with one to three C₁₋₅ branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl or isothiazolyl, each of the
10 aforementioned being substituted with one to five halogen, C₁₋₆ alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, hydroxy, nitrile, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, NH₂C(O), mono- or di(C₁₋₃alkyl)aminocarbonyl; the C₃₋₁₀ branched or
15 unbranched alkenyl being optionally interrupted by one or more heteroatoms chosen from O, N and S(O)_m;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C₁₋₃ alkyl groups;

20 oxo, nitrile, halogen;

silyl containing three C₁₋₄ alkyl groups optionally partially or fully halogenated; or

25 C₃₋₆ alkynyl branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH or S(O)_m and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, hydroxy, pyrroldinyl, pyrrolyl, tetrahydropyranyl, one or more C₁₋₄ alkyl optionally substituted by one or more
30 halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C₁₋₃alkyl)amino optionally substituted by one

or more halogen atoms;

each R₂, R₄, and R₅ is

5 a C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated, C₁₋₆acyl, aroyl, C₁₋₄ branched or unbranched alkoxy, each being optionally partially or fully halogenated, halogen, methoxycarbonyl, C₁₋₃ alkyl-S(O)_m optionally partially or fully halogenated, or phenyl-S(O)_m;

10 OR₆, C₁₋₆ alkoxy, hydroxy, nitrile, nitro, halogen;

or amino-S(O)_m- wherein the N atom is optionally independently mono- or di-substituted by C₁₋₆alkyl or arylC₀₋₃alkyl, or amino wherein the N atom is optionally independently mono- or di-substituted by C₁₋₃alkyl, arylC₀₋₃alkyl, C₁₋₆acyl, C₁₋₆alkyl-S(O)_m- or arylC₀₋₃alkyl-S(O)_m-, each of the aforementioned alkyl and aryl in
15 this subparagraph are optionally partially or fully halogenated and optionally substituted with one to two C₁₋₆ alkyl or C₁₋₆ alkoxy;

each R₃ is independently:

phenyl, naphthyl, morpholino, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl,
20 pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, [1,3,4]oxadiazol, triazolyl, tetrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinoliny, isoquinoliny, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnoliny, pterindiny, phthalazinyl, naphthypyridiny, quinoxaliny, quinazoliny, puriny or indazolyl,
25 each of the aforementioned is optionally substituted with one to three phenyl, naphthyl, heterocycle or heteroaryl as hereinabove described in this paragraph, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅
30 alkyl, halogen, hydroxy, oxo, nitrile, C₁₋₃ alkoxy optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocycloxy wherein

the heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C₁₋₃alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl heterocyclic moiety is as hereinabove described in this paragraph, NH₂C(O), a mono- or di-(C₁₋₃alkyl) aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋₅alkyl)amino, mono- or di-(C₁₋₃alkyl)amino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋₃alkyl)amino-S(O)₂, R₇-C₁₋₅ alkyl, R₈-C₁₋₅ alkoxy, R₉-C(O)-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkyl(R₁₁)N, carboxy-mono- or di-(C₁₋₅alkyl)-amino;

a fused aryl selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heteroaryl selected from cyclopentenopyridinyl, cyclohexanopyridinyl, cyclopentanopyrimidinyl, cyclohexanopyrimidinyl, cyclopentanopyrazinyl, cyclohexanopyrazinyl, cyclopentanopyridazinyl, cyclohexanopyridazinyl, cyclopentanoquinolinyl, cyclohexanoquinolinyl, cyclopentanoisoquinolinyl, cyclohexanoisoquinolinyl, cyclopentanoindolyl, cyclohexanoindolyl, cyclopentanobenzimidazolyl, cyclohexanobenzimidazolyl, cyclopentanobenzoxazolyl, cyclohexanobenzoxazolyl, cyclopentanoimidazolyl, cyclohexanoimidazolyl, cyclopentanthienyl and cyclohexanthienyl; wherein the fused aryl or fused heteroaryl ring is independently substituted with zero to three phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, C₁₋₆ alkyl which is optionally partially or fully halogenated, halogen, nitrile, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocycloxy wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C₁₋₃alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, NH₂C(O), mono- or di-(C₁₋₃alkyl)aminocarbonyl, C₁₋₄ alkyl-OC(O), C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃alkyl)amino-C₁₋₅ alkyl, R₁₂-C₁₋₅ alkyl, R₁₃-C₁₋₅ alkoxy, R₁₄-C(O)-C₁₋₅ alkyl or R₁₅-C₁₋₅ alkyl(R₁₆)N;

cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally be partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S, CHOH, >C=O, >C=S or NH;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, each optionally substituted with one to three C₁₋₃ alkyl groups;

C₁₋₄ alkyl-phenyl-C(O)-C₁₋₄ alkyl-, C₁₋₄ alkyl-C(O)-C₁₋₄ alkyl- or C₁₋₄ alkyl-phenyl-S(O)_m-C₁₋₄ alkyl-;

C₁₋₆ alkyl or C₁₋₆ branched or unbranched alkoxy each of which is optionally partially or fully halogenated or optionally substituted with R₁₇;

OR₁₈ or C₁₋₆ alkyl optionally substituted with OR₁₈;

amino or mono- or di-(C₁₋₅alkyl)amino optionally substituted with R₁₉;

R₂₀C(O)N(R₂₁)-, R₂₂O- or R₂₃R₂₄NC(O)-; R₂₆(CH₂)_mC(O)N(R₂₁)-, R₂₃R₂₄NC(O)-C₁₋₃alkoxy or R₂₆C(O)(CH₂)_mN(R₂₁)-;

C₂₋₆alkenyl substituted by R₂₃R₂₄NC(O)-;

C₂₋₆ alkynyl branched or unbranched carbon chain, optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH, S(O)_m and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, pyrrolidinyl, pyrrolyl, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl one or more C₁₋₄ alkyl

optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C₁₋₄ alkyl)amino optionally substituted by one or more halogen atoms;

5 C₁₋₆acyl or aroyl;

R₆ is a:

C₁₋₄ alkyl optionally partially or fully halogenated and optionally substituted with R₂₆;

10

each R₇, R₈, R₉, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₇, R₁₉, R₂₅ and R₂₆ is independently: nitrile, phenyl, morpholino, piperidinyl, piperazinyl, imidazolyl, pyridinyl, tetrazolyl, amino or mono- or di-(C₁₋₄alkyl)amino optionally partially or fully halogenated;

15

each R₁₁ and R₁₆ is independently:

hydrogen or C₁₋₄ alkyl optionally partially or fully halogenated;

R₁₈ is independently:

20 hydrogen or a C₁₋₄ alkyl optionally independently substituted with oxo or R₂₅;

R₂₀ is independently:

C₁₋₁₀ alkyl optionally partially or fully halogenated, phenyl, or pyridinyl;

25 R₂₁ is independently:

hydrogen or C₁₋₃ alkyl optionally partially or fully halogenated;

each R₂₂, R₂₃ and R₂₄ is independently:

30 hydrogen, C₁₋₆ alkyl optionally partially or fully halogenated, said C₁₋₆ alkyl is optionally interrupted by one or more O, N or S, said C₁₋₆ alkyl also being independently optionally substituted by mono- or di-(C₁₋₃alkyl)aminocarbonyl,

phenyl, pyridinyl, amino or mono- or di-(C₁₋₄alkyl)amino each of which is optionally partially or fully halogenated and optionally substituted with mono- or di-(C₁₋₃alkyl)amino;

or R₂₃ and R₂₄ taken together optionally form a heterocyclic or heteroaryl ring;

5

m = 0, 1 or 2;

W is O or S and

pharmaceutically acceptable derivatives thereof.

10

15) The Pharmaceutical composition according to claim 1, wherein the weight ratios of A to B are in the range from 1:300 to 20:1.

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16) The Pharmaceutical composition according to claim 1 wherein the weight ratios of A to B are in the range from 1:200 to 10:1.

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17) The Pharmaceutical composition according to claim 1, wherein a single application corresponds to a dosage of the active substance combination A and B of about 100 to 10000 µg.

18) The Pharmaceutical composition according to claim 15, wherein a single application corresponds to a dosage of the active substance combination A and B of about 1000 to 9000 µg.

25

19) The Pharmaceutical composition according to claim 1, wherein it is present in the form of a formulation suitable for inhalation.

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20) The Pharmaceutical composition according to claim 19, wherein it is a formulation selected from among inhalable powders, propellant-containing metering aerosols and propellant-free inhalable solutions or suspensions.

- 21) The Pharmaceutical composition according to claim 20, wherein it is an inhalable powder which contains A and B in admixture with suitable physiologically acceptable excipients selected from among the monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts, or mixtures of these excipients with one another.
- 22) The Inhalable powder according to claim 21, wherein the excipient has a maximum average particle size of up to 250µm, preferably between 10 and 150µm.
- 23) The Pharmaceutical composition according to claim 20, wherein it is an inhalable powder which contains only the active substances A and B as its ingredients.
- 24) A Capsule, wherein the capsule contains an inhalable powder according to claim 22.
- 25) The Pharmaceutical composition according to claim 20, wherein it is a propellant-containing inhalable aerosol which contains A and B in dissolved or dispersed form.
- 26) The Pharmaceutical composition according to claim 20, wherein it is a propellant-free inhalable solution or suspension which contains water, ethanol or a mixture of water and ethanol as solvent.
- 27) A method of treating an inflammatory or obstructive disease of the respiratory tract comprising administering to a patient in need thereof a therapeutically effective amount of a composition according to claim 1 .